The acidity and self-catalyzed lactonization of L-gulonic acid: Thermodynamic, kinetic and computational study

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ABSTRACT

Lactonization and proton dissociation of sugar acids take place simultaneously in acidic aqueous solutions. The protonation-deprotonation processes are always fast, whilst the formation and hydrolysis of γ- and δ-lactones are usually slower. Thus, both thermodynamic and kinetic information are required for the complete understanding of these reactions. The protonation constant (K_p) of L-gulonate (Gul⁻) was determined from potentiometric and polarimetric measurements, while the individual lactonization constants ($K_{L,\gamma}$ and $K_{L,\delta}$) for L-gulonic acid (HGul) were obtained *via* ¹³C NMR experiments. The applicability of this method was proven by measuring these well-known constants for D-gluconic acid (HGluc) and by comparing them to literature data. L-gulonic acid γ-lactone (γ-HGul) has remarkable stability in contrast with δ-HGul as well as γ- and δ-HGluc. The polarimetric measurement implies that the main factor responsible for the enhanced stability of γ-HGul is that its hydrolysis is much slower than that of δ-HGul. This higher stability of the γ-HGul ring over its δ-isomer was also confirmed by quantum chemical calculations. A new confirmed feature of the reaction is that in parallel to H₃O⁺, HGul also catalyzes the formation and reverse hydrolytic processes of γ-HGul, similarly to other general acid catalysts.

1. Introduction

Lactones are intramolecular esters of hydroxycarboxylic acids occurring in nature usually as five- (γ) and six-membered (δ) cyclic compounds. They serve as components of various aromas and odors, hence, they are utilized in the cosmetic and food industries. Additionally, important synthetic applications are also known (*e.g.*, ε-caprolactone).

L-gulonic acid and its γ-lactone (HGul and γ-HGul, Scheme 1) are intermediates in the biosynthesis of L-ascorbic acid in mammals [1]. The enzymatic reactions involve the formation of gulonic acid from D-glucuronic acid as discussed in detail in Refs. [2–8]. Nowadays, the industrial production of ascorbic acid is based on the Reichstein process applying the readily available D-glucose instead of D-glucuronic acid [9]. Attempts were also made to obtain ascorbic acid directly from γ-HGul or its 3,5-O-benzylidene derivative [10]. Furthermore, the diol and diisocyanate derivatives of γ-HGul were employed to synthetize polyurethanes [11].

Lactones are formed *via* acid catalysis as follows from the mechanism of the Fischer-Speier esterification [12]. A pioneering work related to the lactonization of HGul and other aldonic acids was carried out by Levene and Simms [13,14]. The five- and six-membered lactones were found to be formed for D-gulonic, D-heptagluconic, D-galactonic, D-gluconic and D-mannonic acids. The authors observed that the the δ-lactone was more dextrorotatory, while the γ-lactone was more levorotatory for the first three aldonic acids. On the other hand, gluconic and mannonic acids could only be converted into dextrototatory lactones.

These observations are formulated in Hudson's lactone rule [15], which stipulates that when the OH group involved in the ring closure lies on the right side on the Fischer projection of the acid, the lactone will be more dextrorotatory, otherwise it will be more levorotatory.
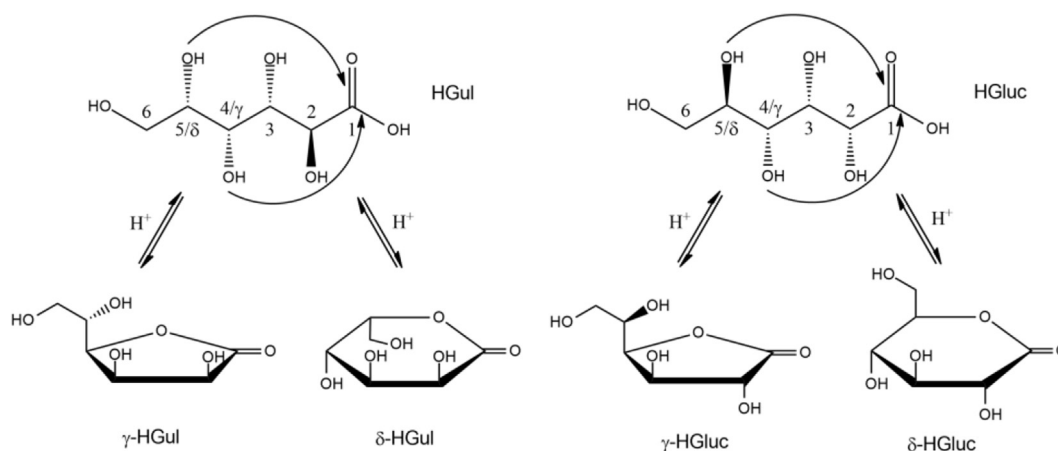
HGul is expected to be a stronger acid than caproic acid owing to the presence of electron withdrawing OH functional groups along the aliphatic backbone. The protonation constant, K_p, of Gul is defined as:

$$K_p = \frac{1}{K_a} = \frac{[\text{HGul}] \cdot c^o}{[\text{H}^+][\text{Gul}^-]} \tag{1}$$

where K_a is the acid dissocation constant of HGul and c^o means the

Scheme 1. Left side: structural formulae of L-gulonic acid (HGul) and its γ- and δ-lactones (γ-HGul, δ-HGul). Arrows indicate the OH groups whose attack on the C1 carbon atom yields the five- or six-membered lactone. Right side: the same for D-gluconic acid (HGluc) are shown for comparison.

standard molar concentration, 1 mol dm^{-3}. At infinite dilution, log K_p^0 of HGul at 25 °C was determined to be 3.67 [13]. The value of log K_p was determined to be 3.48 (I = 0.1 M NaClO$_4$, via potentiometry) [16] as well as 3.20 and 3.19 (I = 1 M NaCl, via ^{1}H and ^{13}C NMR spectroscopies) [17] at 25 °C. For comparison, the log K_p of the caproate ion (same as the pK_a of caproic acid) was reported to be 4.85 [18].

Contrary to gulonic acid, the industrially more important gluconic acid (HGluc, Scheme 1) was studied in great detail previously. The log K_p^0 of HGluc was reported to be 3.77–3.92 [19–21] at 25 °C. At 1 M ionic strength, log K_p was determined to be 3.30–3.63 [21–24] via potentiometry and 3.24 [25] via ^{13}C NMR spectroscopy, respectively.

The work of Levene and Simms is the only one concerning the lactonization of HGul. The initial rate of δ-HGul formation was eight times higher compared to that of γ-HGul at 25 °C [13].

By Baldwin's rules [26], both the reactions resulting the γ- or the δ-lactone (i.e., the 5-exo-trig and the 6-exo-trig types of ring closure) are favoured. The larger stability of the γ-lactone corresponds to the qualitative finding that an exo double bond stabilizes the five-membered ring [27].

The individual lactonization constants of the two isomers are expressed as:

$$K_{L,\gamma} = \frac{[\gamma-\text{HGul}]}{[\text{HGul}]} \tag{2}$$

$$K_{L,\delta} = \frac{[\delta-\text{HGul}]}{[\text{HGul}]} \tag{3}$$

These equilibrium constants can be estimated from the initial rate coefficients of the lacton formation and reverse hydrolysis reported in Ref. [13]. Accordingly, log $K_{L,\gamma} \approx 0.60$ and log $K_{L,\delta} \approx -0.49$. For HGluc, numerous works give quantitative description of the δ-lactonization reaction. The thermodynamic lactonization constant, log $K_{L,\delta}^0$, was calculated to be −0.95 [20] and −0.81 [21]. Depending on the ionic strength and experimental technique used, log $K_{L,\delta}$ ranges from −1.15 to −0.54 [19,21,28–31]. On the other hand, log $K_{L,\gamma}$ was reported to be −0.59 [19] and −0.62 [29]. Clearly, the difference in the stability of the gluconolactones is much smaller compared to that of the gulonolactones.

Contrary to HGluc, quantitative studies for the lactonization reactions of HGul are sporadic. Thus, the available data need to be extended to provide better understanding of the protonation, lactonization equilibria and the lactonization kinetics of this aldonic acid. In this study, we report on the protonation and individual lactonization constants obtained from potentiometric and ^{13}C NMR measurements. The accuracy of the protonation and lactonization constants of HGul were checked by determining these constants also for HGluc and comparing

them with literature data. Additionally, polarimetric experiments and quantum chemical calculations were carried out to characterize the lactonization kinetics and the possible structures of the lactones of HGul present in acidic solutions.

2. Experimental

2.1. Reagents and solutions

All samples were prepared with deionized water (Merck Millipore Milli-Q) and the ionic strength of the solutions was adjusted to 1 M with NaCl (a. r. grade, Molar Chemicals). Stock solutions of HCl were made by volumetric dilution of cc. HCl (a. r. grade, Scharlab), and were standardized against KHCO$_3$. Concentrated ($\approx$50% w/w), carbonate-free NaOH liquor was prepared in-house from pellets (a. r. grade, Analar Normapur) according to the procedure reported previously [32]. The caustic then was brought to volume and the stock solution and it was standardized against HCl solution.

L-gulonic acid γ-lactone (95%, Aldrich), D-gluconic acid δ-lactone ($\geq$99%, Sigma) and sodium D-gluconate ($\geq$99%, Sigma) were used without further purification. The purity of γ-HGul and δ-HGluc was checked by their ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra (0.2 M lactone in 100% V/V D$_2$O, see Figures S1–S4 in the Electronic Supporting Information). Accordingly, contaminants having peak area larger than 1% were not detected. It has to be mentioned that contrary to γ-HGul, large portion of δ-HGluc underwent hydrolysis even in D$_2$O (Figures S3 and S4). The solutions of D-gluconate were made directly from the sodium salt, while those of L-gulonate were prepared by neutralizing the lactone with NaOH until pH $\approx$ 7–8. The completion of ring-opening reaction was confirmed by the ^{1}H and ^{13}C NMR spectra.

2.2. Potentiometric titrations

Potentiometric measurements were carried out with a Metrohm Titrando 888 automatic titration instrument, whilst the cell potentials were recorded with a Jenway 3540 Bench Conductivity/pH Meter using a SenTix 62 combined glass electrode (from WTW). All samples were stirred and thermostated to T = (25.0 ± 0.1) °C during the titrations. To minimize the incidental dissolution of CO$_2$, N$_2$ atmosphere was applied.

The calibration of the electrode was performed by titrating 70 cm^3 solution of 0.02 M NaOH with 0.2 M malonic acid (at 1 M ionic strength). The intercept and slope of the electrode were calculated utilizing the pHCali program [33], and the calibration curve was found to be Nernstian.

To avoid problems associated with the lactonization of HGul and